REMARKS

Applicants acknowledge the allowability of claims 33–53 and 56–62 and submit that all pending claims, including new claims 71–77 are allowable for the reasons stated below.

Claim 4 has been amended more clearly define a sequence of steps. Amended claim 4 is not narrower in scope than the original.

Claims 11–13 have been amended accordingly.

New claims 71–77 define methods specifically for the preparation of N-deacetylate N-sulfate derivatives of K5 polysaccharide. These claims are supported by paragraphs [0058]-[0084] of the published US 2002/62019, in particular

- by paragraph [0070] for claim 71, step (d), and claims 72–74;
- by paragraph [0075] for claim 71, step (e);
- by paragraph [0081] for claims 75–77.

DOUBLE PATENTING (CLAIMS 1–10)

In that the double patenting rejection is only a provisional rejection, applicants submit that this rejection should be withdrawn once the application is otherwise allowable.

This application has an earlier filing date than copending application Serial No. 10/240,606, and a declaration signed by the inventors. The applicants/inventors herein have not authorized the filing of copending application Serial No. 10/240,606. For these reasons, this application should be allowed to issue and subject matter corresponding to claims 1–10 should be canceled from application Serial No. 10/240,606.

CLAIMS REJECTION – 35 U.S.C. § 112

A. Claims 66 and 70 rejection ("prevention of thrombosis")

Applicants respectfully submit that the specification as filed duly supports methods for treating, as well as methods for preventing thrombosis.

From the background of the invention, it is clear an object of the invention is to provide a glycosaminoglycan having a heparin-like structure which is not extracted from animal tissues (as heparin is) but obtained from *E. coli* polysaccharide K5, said glycosaminoglycans also having an heparin-like activity. This purpose is illustrated throughout the description of the prior art.

For one skilled in the art, heparin and heparin-like compounds are known anticoagulant and antithrombotic agents used for both the prevention and the treatment of thrombosis. A MD knows that, in order to prevent possible thromboembolic events for example during surgical operations it is advisable to administer heparin. Analogously, heparin is administered topically for example in order to prevent the formation of leg venous thrombi.

Even though, as the Examiner observes, a preventive use may involve the administration of a drug to a healthy mammal, Applicants respectfully submit that in the case of an antithrombotic agent, in particular of heparin and heparin-like products, said anthithrombotic agent is administered as preventive agent to subjects having a risk of thromboembolic events.

In the cited prior art, Lormeau et al. (US 5,550,116) disclose non-epimerized K5 derivatives and say that the "*compositions are useful for the preventive or curative treatment of disorders of the vascular wall, such as atherosclerosis and arteriosclerosis and of hypercoagulability states observed, for example, following surgical operations*" (see column 13, lines 56-63).

In a review by B. Casu entitled 'Structure and Biological Activity of Heparin' (*Advances in Carbohydrate Chemistry and Biochemistry*, 1985, 43, 51–134), in the first page of the Chapter concerning the biological activity of heparin (page 127), the Author says "*The most widely known biological property of heparin is its anticoagulant activity, currently*

exploited in the prophylaxis and treatment of thrombotic diseases, that is, for preventing formation of thrombi and for achieving regression of thrombi once they are formed.[10,481]".[1]

The introduction of the book 'Low Molecular Weight Heparin' by T.W. Barrowcliffe, 1992, John Wiley & Sons, begins with the sentence "*Low molecular weight heparins are now licensed drugs in several European countries, and they are being increasingly used in the prophylaxis and treatment of venous thromboembolism, as well as in other diseases.*", and ends with "*However, it is already clear that low molecular weight heparin represents a very significant addition to the list of effective drugs used for the prevention and treatment of thrombosis and related conditions.*"

In the instant specification, it is stated that

- the glycosaminoglycans of the present invention are useful, alone or in combination with pharmaceutical excipients or diluents, for the antithrombotic treatment, in particular for the prevention or treatment of thrombosis (see [0171] of the published US 2002/0062019);
- said glycosaminoglycan active ingredient is present in an effective dose for the prevention or treatment of diseases caused by disorders of the coagulation system, such as arterial or venous thrombosis, for the treatment of hematomas or as coagulation controlling agents during surgical operations (see [0182] of the published US 2002/0062019).

These are classical indications for heparin and, hence, for heparin-like, antithrombotic glycosaminoglycans as those disclosed in the instant application which would substitute for the extractive heparin in the prevention or treatment of thrombosis.

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[1] Reference 10: L.B. Jaques, *Pharmacol. Rev.* 31 (1980) 99-166.
Reference 481: D.P. Thomas *Semin. Hematol.* 15 (1978) 1-17;
T.W. Barrowcliffe and D.P. Thomas, *Hemostasis and Thrombosis* Churchill Livingstone, Edinbourgh, 1981, pp. 712-724.

Thus, claims 66 and 70 comply with the requirements of 35 U.S.C. § 112 and Applicants respectfully request that rejection of claims 66 and 70 be withdrawn.

B. Claims 4-34 Rejection (N-sulfation made twice in the process).

Examiner contends that from the wording of claim 4 it is not clear why the same step of N-sulfation is performed twice and that the same recitation is also seen in claims 14 and 17.

Claim 4 as currently amended now clearly separates the distinct steps to be performed sequentially and shows that the process actually includes a N-deacetylation/N-sulfation in step (b) and a final N-sulfation in step (g).

Applicants respectfully submit that, in order to obtain glycosaminoglycans having a heparin-like antithrombotic activity starting from K5 or K5-N-sulfate, the correct sequence (a)-(g) or (i)-(vi) as illustrated in the instant specification must be followed sequentially (see paragraph [0017] of the published US 2002/0062019).

In the description of the prior art, Applicants clearly point out that a considerable amount of N-sulfate groups are lost during O-sulfation of N-sulfated K5 polysaccharides, so that the final compounds obtained in the processes of the prior art do not show satisfactory heparin-like activity (see paragraphs [0010] and [0012] of the published US 2002/0062019).

Also in the summary of the invention, Applicants point out that, thanks to the particular reactions' sequence (i)-(vi) ending with a N-sulfation step, the obtained, novel glycosaminoglycans are almost completely N-sulfated and highly 6-O-sulfated (see paragraph [0017] of the published US 2002/0062019).

The loss of N-sulfate groups during the oversulfation step (d) or (iii) is demonstrated by the complete absence of N-sulfate groups in the O-oversulfated product obtained at the

end of the oversulfation step as shown in paragraphs [0073] and [0116] of the published US 2002/0062019.

In particular, the reason why a final N-sulfation is performed appears in paragraph [0120] of the published US 2002/0062019.

Applicants respectfully submit that the instant specification duly explains the reasons of the final N-sulfation. Thus, a skilled person reading the text of the instant specification, in particular paragraphs [0010] to [0017], [0037] to [0068] and [0102] to [0120] (in particular the last one) of the published US 2002/0062019 is able to understand and interpret claims 4, 14 and 17.

Thus, Applicants ask Examiner to withdraw his rejection of claims 4-34 under 35 U.S.C. § 112.

C. Claims 64 and 68 Rejection (Control of the Coagulation).

Examiner contends that the term "controlling" in claim 64 is a relative term that renders the claim indefinite.

Applicants respectfully submit that the verb "to control" is currently used in the hemobiological field for anticoagulant agents, in particular heparin and heparin-like products which are used for regulating coagulation in individuals with a risk of hypercoagulation. In the context of the claimed invention the skilled artisan realizes, without any possible misunderstanding, that the verb "to control" is used in its meaning "to reduce the incidence or severity of esp. to an innocuous level" (Webster's Third New International Dictionary of the English Language).

A definition of the term "controlling" is not needed in claim 64. The summary (in particular paragraphs [0016]-[0018]) and the detailed description (in particular paragraphs [0094], [0127], [0170], [0171], [0182]) of the invention define the meaning of said term.

An example of the use of the term "controlling" in the coagulation field is also given by the first US patent claiming low molecular weight heparin (Lormeau et al., US 4,692,435) in which a method for controlling thrombosis is also claimed (see claims 4 and 11).

Thus, Applicants respectfully request that the rejection of claims 64 and 68 be withdrawn.

CONCLUSION

In conclusion, with claims 1–77 in condition of allowance, said allowance is respectfully solicited.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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